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SERIAL NUMBER	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.
07/909,379	07/06/92	GOMMELI-MILLIEN	B 5011-1199
		EXAMINER	ZMURKO, M
		ART UNIT	PAPER NUMBER
		2203	6
DATE MAILED: 12/21/92			

This is a communication from the examiner in charge of your application.  
COMMISSIONER OF PATENTS AND TRADEMARKS

This application has been examined  Responsive to communication filed on \_\_\_\_\_  This action is made final.

A shortened statutory period for response to this action is set to expire 3 month(s). \_\_\_\_\_ days from the date of this letter.  
Failure to respond within the period for response will cause the application to become abandoned. 35 U.S.C. 133

Part I THE FOLLOWING ATTACHMENT(S) ARE PART OF THIS ACTION:

1.  Notice of References Cited by Examiner, PTO-892. 2.  Notice re Patent Drawing, PTO-948.  
3.  Notice of Art Cited by Applicant, PTO-1449. 4.  Notice of Informal Patent Application, Form PTO-152.  
5.  Information on How to Effect Drawing Changes, PTO-1474. 6.  \_\_\_\_\_

Part II SUMMARY OF ACTION

1.  Claims 1-16 are pending in the application.  
Of the above, claims 11-16 are withdrawn from consideration.  
2.  Claims \_\_\_\_\_ have been cancelled.  
3.  Claims \_\_\_\_\_ are allowed.  
4.  Claims 1-10 are rejected.  
5.  Claims \_\_\_\_\_ are objected to.  
6.  Claims \_\_\_\_\_ are subject to restriction or election requirement.  
7.  This application has been filed with informal drawings under 37 C.F.R. 1.85 which are acceptable for examination purposes.  
8.  Formal drawings are required in response to this Office action.  
9.  The corrected or substitute drawings have been received on \_\_\_\_\_. Under 37 C.F.R. 1.84 these drawings are  acceptable.  not acceptable (see explanation or Notice re Patent Drawing, PTO-948).  
10.  The proposed additional or substitute sheet(s) of drawings, filed on \_\_\_\_\_ has (have) been  approved by the examiner.  disapproved by the examiner (see explanation).  
11.  The proposed drawing correction, filed on \_\_\_\_\_, has been  approved.  disapproved (see explanation).  
12.  Acknowledgment is made of the claim for priority under U.S.C. 119. The certified copy has  been received.  not been received  been filed in parent application, serial no. \_\_\_\_\_; filed on \_\_\_\_\_.  
13.  Since this application appears to be in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under Ex parte Quayle, 1935 C.D. 11; 453 O.G. 213.  
14.  Other

Restriction to one of the following inventions is required under 35 U.S.C. 121:

- I. Claims 1-10, drawn to a compounds and compositions of formula I, classified in Class 556, subclass 1+.
- II. Claims 11, 13, and 16, drawn to method of enhancing NMR, classified in Class 128, subclass 653.2.
- III. Claims 12 and 14, drawn to method of enhancing X-ray, classified in Class 424, subclass 4.
- IV. Claim 15, drawn to method of radiation therapy, classified in Class 600, subclass 1.

The inventions are distinct, each from the other because of the following reasons:

Inventions of Group I and II-IV are related as product and process of use. The inventions can be shown to be distinct if either or both of the following can be shown: (1) the process for using the product as claimed can be practiced with another materially different product or (2) the product as claimed can be used in a materially different process of using that product (MPEP 806.05(h)). In the instant case the product as claimed can be used in a materially different processes, such as the various methods of use that are claimed by the applicant (e.g. MRI, X-ray, and radiation therapy) and other diagnostic and therapeutic procedures.

Because these inventions are distinct for the reasons given above and have acquired a separate status in the art as shown by their different classification and because of their recognized divergent subject matter, the search for Group I is not required for Groups II-IV, restriction for examination purposes as indicated is proper.

During a telephone conversation with Mr. Anthony J. Zelano on November 18, 1992, a provisional election was made with traverse to prosecute the invention of Group I, claims 1-10. Applicant further elected the species of example 10. Affirmation of this election must be made by applicant in responding to this Office action. Claims 11-16 are withdrawn from further consideration by the Examiner, 37 CFR 1.142(b), as being drawn to the non-elected inventions.

The disclosure is objected to because of the following informalities: the first sentence on page 2 of the specification is incomprehensible. Appropriate correction is required.

The following is a quotation of 35 U.S.C. 103 which forms the basis for all obviousness rejections set forth in this Office action:

A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negated by the manner in which the invention was made.

Subject matter developed by another person, which qualifies as prior art only under subsection (f) and (g) of section 102 of this title, shall not preclude patentability under this section where the subject matter and the claimed invention were, at the time the invention was made, owned by the same person or subject to an obligation of assignment to the same person.

Claims 1-5 and 9-10 are rejected under 35 U.S.C. 103 as being unpatentable over Johnson et al., in view of Troutner et al.

Johnson et al. present an invention that provides bifunctional chelating agents that contain a substrate reactive moiety incorporated into a carboxymethyl arm. Johnson et al. teach in column 3, lines 50-60, "Suitable substrate reactive groups include phenyl groups directly substituted or substituted through aliphatic spacer arms with substrate reactive moieties such as amino,

thiocyanato, diazonium and bromoacetamide which are capable of reacting with one or more functionalities present on the substrate molecule ..." In column 5, Johnson et al. begin to describe the various compounds that their invention pertains to. Note the first structure in column 5 and the various substituents that can be placed on the compound.

Johnson et al. do not teach that the substrate reactive moiety incorporated into a carboxymethyl arm is attached at the  $Z_1$  or  $Z_2$  position of the compound as depicted in the claims presented by the applicants. Troutner et al. teach a group of functionalized triamine chelants and their derivatives that form with radioactive metal ions. In column 2 to column 4, Troutner et al. describe the various compounds that his invention reads upon. Beginning on line 37 of column 2, Troutner et al teach, "R represents independently hydrogen,  $C_{1\text{ to }3}$  alkyl, or benzyl; ..." Troutner et al. continues in column 5, lines 20-23, "The bifunctional chelating agents described herein can be used to chelate or sequester the radioactive metal ions, so as to form metal ion chelates (also referred to herein as 'complexes')." To a person of ordinary skill in the art it would be obvious that the substrate reactive moiety incorporated into a carboxymethyl arm taught by Johnson et al. could be relocated to the positions taught by Troutner et al. These two positions are very closely related as only a single nitrogen atom separates the two. Furthermore, the two side chains taught by Troutner et al. and Johnson et al. are very similar in structure and in purpose as both side chains help form metal ion chelates.

Claims 1-5 and 9-10 are rejected under 35 U.S.C. 103 as being unpatentable over Johnson et al., as mentioned above, in view of Warshawsky et al.

As stated above, Johnson et al. do not teach that the substrate reactive moiety incorporated into a carboxymethyl arm is attached at the  $Z_1$  or  $Z_2$  position of the compound as depicted in the claims

presented by the applicants. Warshawsky et al. teach bifunctional chelating agents which are analogues of EDTA. Refer to column 2, lines 25-46. The 2-substituted ethylenediamine tetraacetic acid compound of type 6 indicates the substrate reactive moiety being incorporated at the Z<sub>1</sub> or Z<sub>2</sub> position of the compound as depicted in the claims presented by the applicants. The compound of type 6 differs in that it does not contain a centrally located nitrogen atom. To a person of ordinary skill in the art it would be obvious that since both of the teachings of Johnson et al. and Warshawsky et al. pertain to similar bifunctional chelating agents (derivatives of EDTA), thus it would be applicable for a skilled artisan to be able to relocate the reactive moiety taught by Johnson et al. to the position taught by Warshawsky et al.

Claims 6-8 are rejected under 35 U.S.C. 103 as being unpatentable over Johnson et al., in view of Troutner et al. or Warshawsky et al., as mentioned above, and in further view of Weber et al.

None of the above teachings, Johnson et al., Troutner et al., or Warshawsky et al., teach that the compound is labeled with gadolinium. Johnson et al. and Troutner et al. teach that the compound is radiolabeled with other metals. Weber et al. disclose a similar structure to the structures claimed by Johnson et al. and Troutner et al. and teaches that the claimed compound can be labeled with various metals. Weber et al. teach in column 2, lines 42-44, "Gadolinium (III) ions have been particularly preferred as NMR image contrasting agents." Thus, to a person of ordinary skill in the art it is obvious that depending upon the particular use of the compound that a multitude of possible metals can be attached for labeling purposes to the compounds claimed by Johnson et al. and Troutner et al., including gadolinium.

The elected species of Example 10 was not found in the prior art.

An inquiry concerning this communication should be directed to Matthew Zmurko at telephone number (703) 308-3957.



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